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(54) Title: PROCESS FOR THE SYNTHESIS OF INTERMEDIATES FOR THE PREPARATION OF ASTAXANTHIN

(57) Abstract: The present invention relates to a process for the preparation of intermediates useful in the synthesis of Astaxanthin, in particular C_{15}-Wittig salts, but also 4-oxo-β-ionones, 3-hydroxy-4-oxo-β-ionones and the aryl esters thereof. 4-oxo-β-ionone is prepared by starting from a β-ionone by oxidation with bromates in the presence of iodine or iodide. 3-hydroxy-4-oxo-β-ionone is prepared in 4 steps, starting from 4 -oxo- β-ionone by oxidation with peracids; the aryl esters thereof are solids that are easily isolated and purified by crystallisation, and may be converted in 5 steps to C_{15}-Wittig salts and finally, by the Wittig reaction, to Astaxanthin.

Process for the synthesis of intermediates for the preparation of astaxanthin

Technical field of the invention

The present invention relates to a process for the preparation of intermediates useful in the synthesis of Astaxanthin, in particular C_{15}-Wittig salts, but also 4-oxo-β-ionones, 3-hydroxy-4-oxo-β-ionones and the aryl esters thereof.

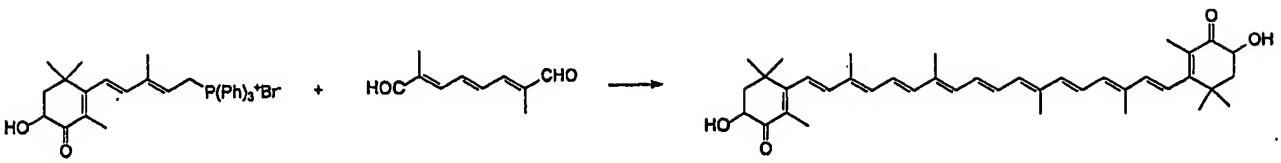
State of the art

Astaxanthin is a carotenoid found widely throughout nature (for example it is present as a pigment in numerous crustaceans) and is of significant commercial interest as a food additive; it is mainly used as a natural food-colouring for fish, in order to give the flesh a colour similar to that of salmon (for example salmon trout). Even though initially, Astaxanthin was extracted from crushed crustacean shells, given the rather large quantities required on the global market, which is in continual expansion, it is currently more often produced by chemical synthesis.

All the major synthetic pathways for Astaxanthin 1 use two chemical synthons in the last step known as C_{15}-Wittig salts 2 and C_{10}-dialdehydes 3 (see scheme 1),

which condense together through the Wittig reaction to give the final product.

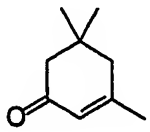
Scheme 1



2 3 1

The C_{10}-dialdehyde intermediate 3 may be prepared by following the indications given in the UK patent GB 768172.

On the other hand, synthesis of the C_{15}-Wittig salt intermediate 2 is rather more difficult. The current industrial synthetic processes for this intermediate start from a cheap and commercially available raw material known as isophorone, which has the following formula:

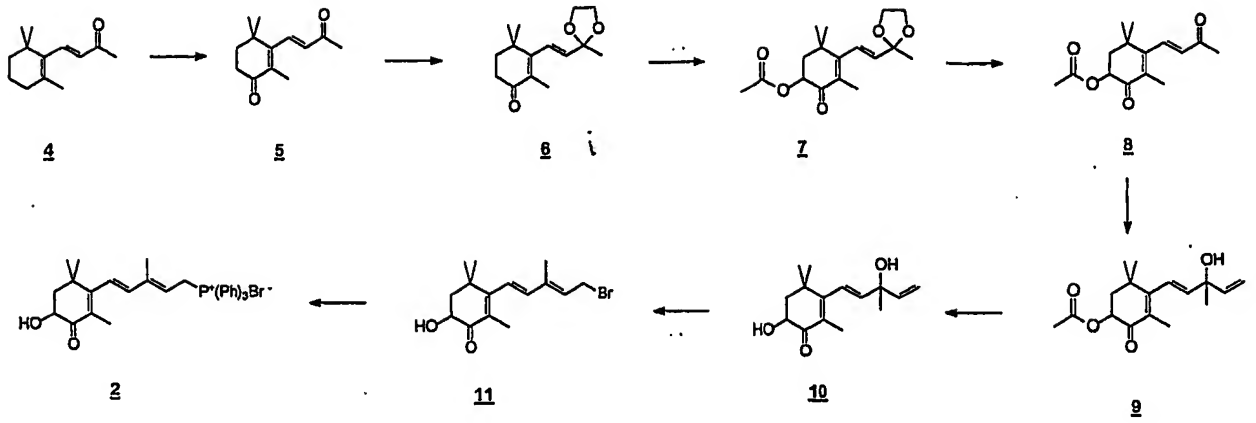


This is a complex multi-step process which also uses several raw materials and/or intermediates which have chemical stability and toxicity problems.

Another interesting synthetic approach (see schema 2), described in Helv. Chim. Acta. 64 (1981), 2419-2435

and EP 5749, on the other hand uses β-ionone 4, a relatively cheap raw material that is available commercially, which also has the advantage of having a 15 carbon atom backbone, much more complex than that of isophorone and having a chemical structure much closer to that of a Wittig salt 2. β-ionone 4 is oxidised to 4-oxo-β-ionone 5, then transformed into the corresponding monoketal 6, then oxidised in the presence of excess lead tetra-acetate in toluene to give 3-acetoxy-4-oxo-β-ionone monoketal 7 and then finally de-protected to give 3-acetoxy-4-oxo-β-ionone 8 with an overall yield of 58% from 6. In the second part of the synthetic process, the key reaction is the transformation of 3-acetoy-4-oxo-β-ionone 8 into the intermediate 9, which is then converted to the Wittig salt 2 by hydrolysis of the ester, rearrangement of the tertiary alcohol 10 to the corresponding allyl bromide 11 and finally reaction with triphenylphosphine.

Scheme 2



However, 4-oxo-β-ionone **5** is obtained with modest yield (52%) from β-ionone **4** by oxidation with pyridinium chlorochromate (PCC) in DMSO. Furthermore, this process has additional problems for its industrial application: firstly, the use of rather toxic and highly polluting chromium(VI)-based oxidants, and the purification of a number of intermediates by silica gel chromatography, a costly technique, and difficult to apply on a large industrial scale.

In the literature, there are other methods for the direct oxidation of β-ionone **4** to 4-oxo-β-ionone **5**, but they generally make use of reagents that are infeasible for industrial production, such as ceric ammonium nitrate and iodine (Chem. Express (1991), 6(2), 125-8), or chromium(VI) derivatives (Tetrahedron

(1992), 48(5), 953-62); in any case, the yields obtained rarely exceed 50%.

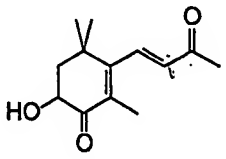
Furthermore, in the literature, there are several processes for the indirect oxidation of β-ionone. The work published in J. Chem. Soc. 1951, 1074 makes use of allylic bromination using NBS and oxidation with manganese dioxide, but the process requires 4 steps and the overall yield is low. In J. Am. Chem. Soc., 2003, 125, 3232-3233 α,β-enones are oxidised with high yield (80-90%) to 1,4-dienones in heterogeneous phase with t-butyl hydroperoxide and palladium hydroxide on carbon; however, the application of this method to β-ionone 4 has lead to a mixture of products, including 4-oxo-β-ionone 5 in percentages of less than 40%.

Finally, US patent US 4209450 claims a process in which β-ionone 4 is oxidised directly to give 4-oxo-β-ionone 5 by means of a biphasic chloroform/aqueous sulphuric acid system, using as an oxidant a large excess of sodium chlorate, in the presence of catalytic quantities of iodine or sodium iodide: following reaction for 24 hours at 45°C, the product is isolated initially as a crude oil with a yield of 56% and subsequently purified by high vacuum fractional distillation to give 4-oxo-β-ionone 5 with a final yield of 40%. However, repetition of the

procedure reported in the aforementioned patent has not lead to the attainment of significant quantities of product (see example 1).

Hence, there is nothing in the literature describing a synthetic process allowing the attainment of 4-oxo-β-ionone **5** by means of an industrially applicable process, *i.e.* characterised by acceptable yields, the use of cheap and non-toxic raw materials and a process that is simple and easy to industrialise.

In relation to the synthesis of 3-acetoxy-4-oxo-β-ionone **8** and the corresponding alcohol 3-hydroxy-4-oxo-β-ionone **12**, the only synthetic pathway described in the literature is that reported in Helv. Chim. Acta 64 (1981), 2419-2435 and EP 5749 (see scheme 2).



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This pathway has significant problems in relation to its industrial application, associated primarily with the use and the disposal of lead tetra-acetate. Furthermore, the intermediate 3-acetoxy-4-oxo-β-ionone **8** has the characteristic of being a low melting point solid that is difficult to purify on the industrial scale. The US patent US 4963583 describes and claims esters of 3-hydroxy-4-oxo-β-ionone **12**, that can be

used as antifungal agents, wherein the ester moiety is represented by an alkyl, cycloalkyl or alkoxyalkyl chain. In any case, this patent reports that compound **12** is prepared according to the directions in Helv. Chim. Acta. 64 (1981), 2419-2435 and EP 5749 (US 4245109).

However, there are no reports in the literature of an oxidation method for 4-oxo-β-ionone **5** to give 3-hydroxy-4-oxo-β-ionone **12** and the esters thereof which can be applied industrially.

Furthermore, to date, there are no synthetic pathways available starting from β-ionone for the intermediate C_{15}-Wittig salt **2** which can conveniently be applied industrially.

Brief description of the invention

The present invention relates to a process for the preparation of astaxanthin wherein the distinguishing feature is the process for the preparation of a C_{15}-Wittig salt **2** starting from a β-ionone **4**, through the intermediates 3-hydroxy-4-oxo-β-ionone **12** and the aryl esters thereof. Said process is characterised by the use of cheap and non-toxic raw materials, it is simple and easily industrialisable and gives good molar yields. Furthermore, the aryl esters of 3-hydroxy-4-oxo-β-ionone **12** have the characteristic of being

relatively high melting point solids, and can be purified by simple crystallisation from the corresponding reaction mixture and thus be obtained with such a degree of purity as to be able to be conveniently used in the synthesis of the intermediate C_{15}-Wittig salt **2** and thus Astaxanthin **1**. In the process of the invention, the β-ionone **4** is oxidised to 4-oxo-β-ionone **5** by means of a particularly advantageous method.

Detailed description of the invention

Synthesis of the C_{15}-Wittig salt **2**

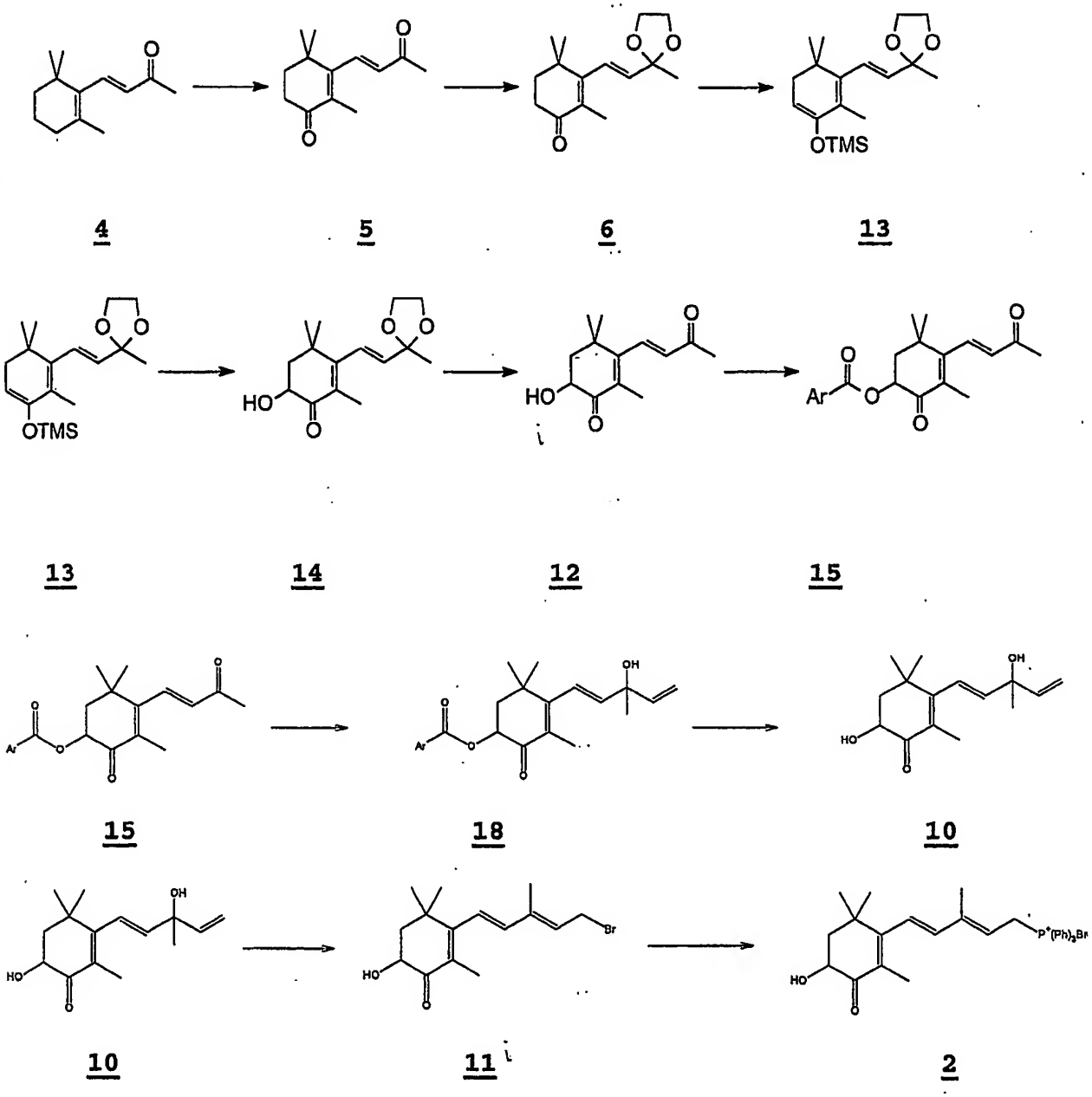
It has surprisingly been found that it is possible to efficiently prepare the key intermediate for the synthesis of Astaxanthin **1**, *i.e.* the C_{15}-Wittig salt **2**, starting from a β-ionone **4**.

According to one first aspect of the invention, the process comprises an oxidation step of the β-ionone which allows it to be obtained with high yield.

According to another particularly preferred aspect, the process comprises ten synthetic steps, but with the isolation of just two solid intermediate, namely the 4-oxo-β-ionone **5** and the aryl ester of the 3-hydroxy-4-oxo-β-ionone **15** (see scheme 3). The C_{15}-Wittig salt **2** is then used for the synthesis of Astaxanthin **1** according to the synthetic scheme known

in the art, *i.e.* through a Wittig condensation reaction with a C_{10}-dialdehyde **3** (see schema 1).

Schema 3



4 **5** **6** **13**

13 **14** **12** **15**

15 **18** **10**

10 **11** **2**

Synthesis of 4-oxo-β-ionone 5

It has surprisingly been found that it is possible to oxidise β-ionone 4 to 4-oxo-β-ionone 5, directly and with good yield, using an alkaline metal or alkaline earth metal bromide as an oxidant in the presence of catalytic quantities of iodine or an alkaline metal or alkaline earth metal iodide and operating in an inert organic solvent in an acidic aqueous medium, which allows the *in situ* formation of bromic and/or iodic acid. The reaction is easily achieved by adding the bromate solution to the mixture constituted by the β-ionone 4 dissolved in the organic solvent and an aqueous solution of iodide and acid.

The bromate used is preferably selected from sodium bromate, potassium bromate and calcium bromate, more preferably sodium bromate. For a better outcome of the oxidation reaction, it is important that the quantity of bromate used preferably be between 0.5 and 1.5 equivalents, more preferably between 0.9 and 1.1 equivalents.

The iodide used is preferably selected from sodium iodide and potassium iodide, and the quantity thereof is preferably between 0.05 and 1.0 equivalents, more preferably between 0.05 and 0.2 equivalents.

The organic solvent is selected from aliphatic and aromatic hydrocarbons, ethers and esters, chlorinated hydrocarbons, alcohols and polar aprotic solvents, preferably from hexane, cyclohexane, toluene, t-butyl methyl ether, THF, ethyl acetate, isopropyl acetate, methylene chloride, chloroform, chlorobenzene, dimethyl sulphoxide and methanol, more preferably methylene chloride.

Depending on the organic solvent used, the reaction is carried out at a temperature between 0 and 100°C, preferably between 20 and 70°C, more preferably between 30 and 40°C. The reaction time is generally between 1 and 8 hours.

The acidic aqueous medium is constituted by dilute aqueous solutions of mineral or organic acids, acid salts or a mixture of an acid and its corresponding salt so as to form a buffer solution. The acid is an inorganic acid, preferably selected from sulphuric acid, hydrochloric acid, phosphoric acid, sodium bisulphate, more preferably sodium bisulphate, or an organic acid, preferably selected from acetic acid, formic acid and citric acid. The quantity of acid is preferably between 0.1 and 1.0 equivalents, more preferably between 0.1 and 0.4 equivalents.

It has been observed experimentally that the oxidation reaction is more selective and clean when using aqueous solutions of relatively weak mineral acids, just like sodium bisulphate, where the system is buffered to pH 2-3 during the course of the entire reaction.

Using an aqueous solution of sodium bisulphate, sodium bromate and potassium iodide and methylene chloride, and with careful selection of the reaction conditions, it is possible to achieve more or less complete conversion (greater than 95%) with a percentage of 4-oxo-β-ionone **5** in the reaction mixture between 80% and 90%. The work-up comprises washing the aqueous phase with an aqueous solution of sodium bisulphite and sodium hydroxide, so as to reduce the iodine once more to iodide and break down any excess oxidant still present. The 4-oxo-β-ionone **5** is finally isolated by separation of the aqueous phase and evaporation of the organic solvent, and obtained with an overall yield between 85% and 95% and purity generally in excess of 90%.

The product may be purified by crystallisation from a suitable apolar organic solvent, preferably selected from pentane, hexane, heptane, or mixtures of the isomers thereof, more preferably a heptane isomer

mixture, and obtained with a yield between 70% and 80% with respect to β-ionone 4 and purity in excess of 97%.

The aforementioned process has undoubted advantages with respect to that described in the US patent US 4209450 for the more or less quantitative conversion, the yield greater by at least 30 percentage points, the use of a stoichiometric quantity of oxidant and the much shorter reaction times. The process is furthermore characterised by the use of cheap, easily available, non-toxic raw materials, by simple execution and by high yield, all of which make it industrially applicable.

Synthesis of 3-hydroxy-4-oxo-β-ionone 12 and the aryl esters thereof

4-oxo-β-ionone monoketal 6 is prepared by reacting 4-oxo-β-ionone 5 with ethylene glycol in the presence of an acid catalyst and a dehydrating agent. The acid catalyst is an inorganic or organic acid, preferably selected from sulphuric, hydrochloric, hydrobromic, methanesulphonic and p-toluenesulphonic acid, more preferably p-toluenesulphonic acid. The dehydrating agent is preferably an orthoformate or an orthoacetate, more preferably trimethyl orthoformate.

It has surprisingly been found that it is possible to oxidise 4-oxo-β-ionone monoketal **6** to 3-hydroxy-4-oxo-β-ionone **12** avoiding the use of toxic oxidising agents. As reported in scheme 3, compound **6** is converted into the corresponding trimethylsilylenolether **13**, which is oxidised by an organic peracid to give 4-oxo-β-ionone monoketal **14**, which is directly de-protected during the reaction acid work-up to give 3-hydroxy-4-oxo-β-ionone **12**. The reaction sequence may be conveniently carried out by applying the so-called "telescoping" principle, i.e. without the isolation of the reaction intermediates **13** and **14**.

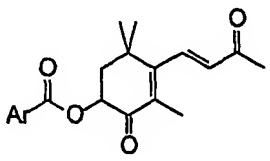
The reaction for the formation of trimethylsilyloxy-β-ionone 9-ethylene ketal **13** may be conveniently carried out using a silanising agent preferably selected from chlorotrimethylsilane, bromotrimethylsilane, iodotrimethylsilane and hexamethyldisilazane, more preferably chlorotrimethylsilane, and an organic and organometallic base, preferably selected from triethylamine, diisopropylethylamine, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, more preferably lithium diisopropylamide. The lithium diisopropylamide may be prepared conveniently and

economically *in situ* by reacting diisopropylamine and n-butyl lithium.

The oxidation reaction to 3-hydroxy-4-oxo-β-ionone **12** is carried out using a peracid, preferably selected from peracetic acid, m-chloroperbenzoic acid, potassium monoperoxyphthalate, more preferably peracetic acid, or a peroxide or a hydroperoxide. The solution of peracetic acid in acetic acid is a commercially available and very economical substance. The reaction may be conveniently carried out in an organic solvent that is immiscible with water, preferably selected from aliphatic and aromatic hydrocarbons and chlorinated hydrocarbons, more preferably selected from toluene, xylene, methylene chloride, chloroform, even more preferably in toluene. The intermediate 3-hydroxy-4-oxo-β-ionone **12** is obtained after evaporation of the solvent as a crude oil with an overall 4-oxo-β-ionone **5** yield of 90-100% and purity of 65-75% (by HPLC), corresponding to a molar weighted yield (HPLC wt %) of 60-65%. If desired, the intermediate may be purified by high vacuum distillation, but the purity of the crude product is sufficient for its use in the synthesis of the ester derivatives thereof.

The aforementioned oxidation method allows the attainment of 3-hydroxy-4-oxo-β-ionone **12** by means of a process that is significantly improved with respect to that described in Helv. Chim. Acta. 64 (1981), 2419-2435 and EP 5749, in that it is characterised by superior yield and above all by the use of non-toxic raw materials without the environmental and disposal problems, a factor which is important for a process which is to be applied industrially.

It has furthermore surprisingly been found that the esters of 3-hydroxy-4-oxo-β-ionone **12** of general formula **15**



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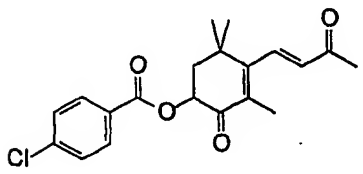
wherein Ar is an optionally substituted aryl or heteroaryl group, are generally solid substances, some relatively high-melting and stable indefinitely under normal conditions. Furthermore, they can be isolated by simple crystallisation from the corresponding reaction mixture and therefore can be obtained with such a degree of purity as to be able to be used in

the synthesis of the intermediate C_{15}-Wittig salt **2** and therefore of Astaxanthin **1**.

Ar is a phenyl group, optionally mono- or polysubstituted with groups preferably selected from alkoxyl, halogen, nitro, cyano and methyl, or a polyaryl group, preferably naphthyl. More preferably Ar is a phenyl group, monosubstituted with a halogen or nitro, even more preferably with a chlorine atom. Particularly preferred compounds include 3-(4-chlorobenzoyloxy)-4-oxo-β-ionone of formula **16** and 3-(1-naphthoyloxy)-4-oxo-β-ionone of formula **17**.



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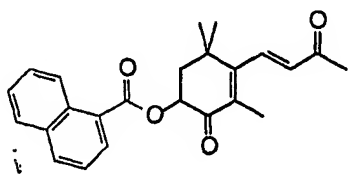

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These aryl esters may be synthesised starting from 3-hydroxy-4-oxo-β-ionone **12**, using compounds of formula ArCOX, wherein Ar has the same meaning as above and X is selected from a halogen and R_1COO-, wherein R_1 is an alkyl or aryl group, optionally substituted with a substituent that is the identical to or different from Ar. Preferably, acyl halides are used, wherein X is a

halogen, in that it is more reactive and more economical than the corresponding anhydrides of formula $(ArCO)_2O$ or mixed anhydrides of formula $ArCO\text{-}O\text{-}COR_1$, wherein R_1 is different from Ar, but sterically hindered. In the case where acyl halides are used, a base is used as a hydrohalo acid acceptor which develops, preferably selected from a tertiary amine, for example pyridine or triethylamine, and an inorganic base in aqueous solution, thus operating under Schotten-Baumann conditions. The synthesis is conveniently carried out starting from a solution of 3-hydroxy-4-oxo-β-ionone **12** in a suitable inert organic solvent, such as for example toluene, containing a stoichiometric quantity of triethylamine and a catalytic quantity of 4-dimethylaminopyridine to accelerate the reaction. The product may be isolated with good yield and chemical purity by crystallisation from common organic solvents, preferably from alcoholic solvents, more preferably from methanol, ethanol and isopropanol.

3-(4-chlorobenzoyloxy)-4-oxo-β-ionone **16** is a solid, relatively high-melting product (m.p. 128-132°C), that can be easily synthesised starting from crude 3-hydroxy-4-oxo-β-ionone **12** and 4-chlorobenzoyl chloride, a cheap raw material that is easily

available commercially. The product is easily crystallised from methanol and obtained with an overall 4-oxo-β-ionone **5** molar yield of 45-55% and purity generally in excess of 98% (by HPLC). 3-(4-chlorobenzoyloxy)-4-oxo-β-ionone **16** has been shown to be a particularly useful intermediate for the preparation of the C_{15}-Wittig salt **2** and hence Astaxanthin 1.

Besides 3-(4-chlorobenzoyloxy)-4-oxo-β-ionone **16**, other aryl esters of formula **15** useful for the synthesis of Astaxanthin **1** have been synthesised: benzoyl, 2-bromobenzoyl, 2-nitrobenzoyl, 3-chlorobenzoyl, 3,4-dichlorobenzoyl, 2-naphthoyl and 1-naphthoyl esters.

The esters of 3-hydroxy-4-oxo-β-ionone **12** of general formula **15** are then converted in five steps to the C_{15}-Wittig salt **2** and, thereafter, to Astaxanthin 1 according to published procedures. Indeed, such esters are alkylated by reaction with a Grignard or lithium salt of acetylene in order to obtain the corresponding tertiary alcohol, which is selectively reduced by hydrogenation catalysed by $Pd/CaCO_3$ (Lindlar) in order to obtain the esters of C_{15}-vinylionol of general formula **18**. The ester bond is hydrolysed under basic conditions in order to give C_{15}-

vinylionol **10**, which is then reacted with concentrated hydrobromic acid to give allylic transposition and bromination. The C_{15}-allylbromide of formula **11** is converted by reacting with triphenylphosphine to give the C_{15}-Wittig salt **2**. The two synthons, denominated C_{15}-Wittig salt **2** and C_{10}-dialdehyde **3** (see scheme 1) are converted into Astaxanthin **1** according to the instructions reported in Helv. Chim. Acta. 64 (1981), 2419-2435 and EP 5749 by double Wittig reaction in isopropanol in the presence of butylene oxide or, equivalently, in methanol in a basic environment.

In conclusion, the synthetic process forming the subject of the present invention, allows the attainment of the C_{15}-Wittig salt **2** by using a multi-step synthetic pathway, but consisting of the isolation of just two solid intermediates, namely the 4-oxo-β-ionone **5** and the ester of 3-hydroxy-4-oxo-β-ionone **15**. The process is likewise characterised by good overall molar yield, by the use of raw materials that are easily obtainable in industrial quantities, and are cheap and non-toxic, by limited environmental impact, so that all the waste products obtained may be disposed of by means of standard incineration plants or biological treatment, and by no means least, simple execution and correct volumetry; all these aspects

making the process industrially applicable for the production of Astaxanthin.

Examples

Example 1 (comparative): 4-oxo-β-ionone 5

By following the instructions in example 1 of US patent US 4209450, a round-bottomed flask, under an atmosphere of nitrogen, is loaded with 4.8 g of β-ionone (25 mmol) and 125 mL of chloroform, then 13.3 g of sodium chlorate (125 mmol, 5 eq.) and 0.56 g of sodium iodide (3.7 mmol) dissolved in 50 mL of water are added. The solution is acidified with 55 µL of concentrated sulphuric acid. The reaction mixture is heated at 45°C for 24 hours, and the progress of the reaction monitored by GC/HPLC. 2 hours after addition, there are no traces of product in the reaction mixture, and after 24 hours, there is only 6.8%.

Example 2: 4-oxo-β-ionone 5

Into a suitable reaction vessel, under an atmosphere of nitrogen, is loaded 100 g of 4-oxo-β-ionone (520 mmol) and 500 mL of methylene chloride; the reaction mixture is heated at 37°C and in the meantime a solution containing 9.6 g of potassium iodide (58 mmol) dissolved in 60 mL of water added, followed by a solution containing 17 g of sodium bisulphate monohydrate (123 mmol) dissolved in 35 mL of water. A

solution containing 79.2 g of sodium bromate (525 mmol), dissolved in 250 mL of water, is added dropwise at 35-40°C over as period of 2.5 hours. The reaction mix is stirred at 35-40°C for 4 hours and the progress of the reaction monitored by GC/HPLC. Upon completion of the reaction, the system is cooled to 25°C, the acidic aqueous phase separated and the organic phase treated with a solution containing 31 g of sodium hydroxide in 200 mL of water, then with a solution of 15.6 g of sodium hydroxide in 100 mL of water, then with a solution containing 15.0 mL of acetic acid and 1.5 g of sodium bisulphite in 100 mL of water and finally with 100 mL of water. The organic phase is treated with 10 g of acticarbone, filtered, and then concentrated to a residue under vacuum. 400 mL of heptane isomer mixture are added and the suspension heated to 35-40°C, then cooled to 0°C: the 4-oxo-β-ionone precipitate is then filtered, washed with 80 mL of heptane and then dried to constant weight under vacuum at 25-30°C, to give 80.5 g of 4-oxo-β-Ionone (75%) with purity (as judged by HPLC) > 97%.

Example 3: 4-oxo-β-ionone 9-ethylene ketal 6

Into a suitable reactor under nitrogen is loaded 80.5 g of 4-oxo-β-ionone (390 mmol), 45 mL of methylene chloride and 161 mL of ethylene glycol (2.88 mol). The

suspension is stirred at RT for 30', then 0.74 g of p-toluenesulphonic acid (3.90 mmol) added. A solution constituted by 50.5 mL of trimethyl orthoformate (460 mmol) and 0.105 mL of pyridine (1.3 mmol) is added dropwise at 20-25°C over a period of 30-40'. Upon completion of the reaction (GC) the reaction mixture is poured into a mixture constituted by 9.65 g of sodium carbonate dissolved in 80 mL of water and 80 mL of heptane isomer mixture. The phases are separated and the aqueous phase extracted twice with 80 mL of heptane and the organic phases washed twice with 80 mL of water. The organic phase is cooled to 10°C and treated with a solution of 68 mL of methanol, 130 mL of water with 11 mL of glacial acetic acid, while the temperature is maintained at 10°C. After 7 hours, GC analysis shows the quantity of 4-oxo-β-ionone 9-ethylene ketal present to be 92-93%. The mixture is poured into a solution of 25.7 g of sodium carbonate in 225 mL of water. The aqueous phase is separated and the organic phase treated with 8.05 g of anhydrous sodium sulphate and 8.05 g of acticarbone, the suspension is stirred at RT for 30' and then filtered. The solution is evaporated to half volume (the solution can contain at most 1 volume of heptane) and is used as such in the subsequent reaction.

Example 4: 4-trimethylsilyloxy-β-ionone 9-ethylene ketal **13**

Into a carefully dehydrated suitable reaction vessel under nitrogen is added 66 mL of diisopropylamine (468 mmol) and 95 mL of tetrahydrofuran. A solution of 165 mL of 25% n-butyl lithium in heptane (460 mmol) is added dropwise at 20°C over 45-60'. The reaction mixture is stirred at 20° for 30', then the solution containing the crude 4-oxo-β-ionone 9-ethylene ketal obtained according to example 3 is added dropwise over 1 hour at 20-25°C. After 45', 61 mL of chlorotrimethylsilane (456 mmol) is added over 30-40 min. at 20-25°C. The reaction mixture is stirred for at least 30' under nitrogen, then the solvent is evaporated under vacuum to leave a dense residue, which is then diluted with 160 mL of toluene; the inorganic salts present are filtered and washed with toluene. The solution containing crude 4-trimethylsilyloxy-β-ionone 9-ethylene ketal is stored under nitrogen and used directly in the following step.

Example 5: 3-hydroxy-4-oxo-β-ionone **12**

Into a suitable reaction vessel, under an atmosphere of nitrogen, is loaded 106 mL of paracetic acid in 32% acetic acid (507 mmol) and 160 mL of toluene; the

temperature of the mixture is adjusted to -15°C, and at that temperature, the toluene solution containing crude 4-trimethylsilyloxy-β-ionone 9-ethylene ketal prepared in example 4 is added dropwise over 1-3 hours. The reaction mixture is stirred at T < -10°C for one hour and, upon completion of the reaction, a solution of 6.1 mL of 32% hydrochloric acid in 80 mL of water added. The reaction mix is stirred for 1.5 hours then neutralised with approx. 190 mL of 30% sodium hydroxide. The organic phase is separated and the aqueous phase is extracted with 60 mL of toluene; the combined organic phases are washed with a 80 mL solution containing 1.6 g of sodium bisulphite in water (15 mmol). The organic phases are dried by evaporation of approx. 1/3 of the solvent present, so as to obtain a clear solution, which is used directly in the following step.

Example 6: 3-(4-chlorobenzyloxy)-4-oxo-β-ionone **16**

Into a suitable reaction vessel, under a nitrogen atmosphere, is loaded, the toluene solution of 3-hydroxy-4-oxo-β-ionone prepared according to example 5, 51.5 mL of triethylamine and 0.80 g of 4-dimethylaminopyridine; 41.5 mL of p-chlorobenzoyl chloride is added dropwise at 20-25° over the course of one hour and the reaction mix stirred for 3-4

hours. Upon completion of the reaction 80 mL of water are added and the mixture heated at 40°C for 30'. The p-chlorobenzoic anhydride by-product is eliminated by filtration while hot. The organic phase is separated and the aqueous phase subsequently extracted with 60 mL of toluene. The combined organic phases are concentrated to residue under vacuum, taken up with 135 mL of methanol and the solvent evaporated once more under vacuum. The solid residue is then taken up with 400 mL of methanol and 1 mL of triethylamine; the suspension is then refluxed and stirred so as to give a solution which is gradually cooled to 0°C, thus achieving the precipitation of the product. The precipitate is filtered, washed with 75 mL of cold methanol and dried to constant weight, 73.2 g of 3-β-chlorobenzyloxy)-4-oxo-β-ionone are obtained (52% with respect to 4-oxo-β-ionone), m.p. = 128-132°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.22 (s, 3H, CH_3 (1_a) ring) ; 1.42 (s, 3H, CH_3 (1_b) ring) ; 1.85 (d, 0.9 Hz, 3H, CH_3(5)ring); 2.15-2.30 (m, 2H, CH_2 (2) ring) ; 2.36 (s, 3H, CH_3 chain) ; 5.76 (dd, 1H, 3 Hz, 12 Hz, CH(3)ring); 6.24 (d, 1H, 16.5 Hz, CH_{vin} C=O); 7.23 (dd, 1H, 0.9Hz; 16.5Hz, CH_{vin} chain); 7.41-7.44 (m, 2H, 3,3' Ph); 8.01-8.04 (m, 2H, 2,2' Ph).

^{13}C-NMR (75 MHz, $CDCl_3$) : δ (ppm) = 13.6; 25.9; 28.2; 30.1; 37.0; 42.7; 71.5; 128.1; 128.7; 130.3; 131.3; 134.1; 139.2; 139.7; 157.2; 165.0; 193.4; 197.7

Example 7: 3-hydroxy-4-oxo-β-ionone **12**

Into a suitable reactor under nitrogen are loaded 234 g of 4-oxo-β-ionone (1.135 mol), 130 mL of methylene chloride and 468 mL of ethylene glycol (8.38 mol). The suspension is stirred at RT for 30', then 2.15 g of p-toluenesulphonic acid (11 mmol) added. A solution constituted by 180 mL of trimethyl orthoformate (1.644 mmol) and 0.305 mL of pyridine (3.8 mol) is added dropwise at 20-25°C over a period of 30-40'. Upon completion of the reaction (GC) the reaction mixture is poured into a solution constituted by 28.0 g of sodium carbonate, 235 mL of water and 235 mL of heptane isomer mixture. The organic phase is separated and the aqueous phase extracted twice with 235 mL of heptane and the organic phases washed twice with 235 mL of water. The organic phase is cooled to 10°C and treated with a solution of 200 mL of methanol, 375 mL of water with 32.5 mL of glacial acetic acid (567 mmol), while the temperature is maintained at 10°C. Generally, after 5 hours, the 4-oxo-β-ionone 9-ethylene ketal **6** reaches a quantity in excess of 90% (as judged by GC). The mixture is poured into a

solution of 74.7 g of sodium carbonate in 655 mL of water, the phases are separated and the organic phase treated with 23.4 g of anhydrous sodium sulphate and 23.5 g of acticarbone; the suspension is stirred at 20-25° C for 30' and then filtered. The solution is evaporated to half volume, to give 430 g of heptane solution which is added under nitrogen to a solution of lithium diisopropylamide, previously prepared by treating 192 mL of diisopropylamine (1.362 mol) in 280 mL of tetrahydrofuran at 20°C with a solution of 480 mL of 25% n-butyl lithium in heptane (1.339 mol). The resulting solution is stirred for 45' at 20°C, then 177 mL of chlorotrimethylsilane (1.170 mol) added dropwise at 20-25°C over 40'. The reaction mix is stirred for 30', then the solvent evaporated under vacuum to a dense residue, which is then diluted with 460 mL of toluene; the inorganic salts present are filtered and washed with 180 mL of toluene. The resulting solution is transferred under an atmosphere of nitrogen into a dropping funnel and then added, over the course of an hour, to a mixture thermostated at -15°C consisting of 310 mL of peracetic acid in 32% acetic acid (1.475 mol) and 160 mL of toluene. Upon completion of the reaction, 12 mL of 32% hydrochloric acid in 235 mL of water are added. The reaction mix is

stirred for 1.5 hours, then, upon completion of the reaction (as judged by HPLC analysis) neutralised with approx. 320 mL of 30% sodium hydroxide. The organic phase is separated and the aqueous phase is extracted with 175 mL of toluene; the combined organic phases are washed with a 235 mL solution containing 4.6 g of sodium bisulphite in water (45 mmol). The organic phase is concentrated to an oily residue, to give 135 g of crude 3-hydroxy-4-oxo-β-ionone (53% with respect to 4-oxo-β-ionone) with a purity of 65% (as judged by HPLC), which is then used crude directly in the subsequent esterification reactions.

Example 8: 3-(1-naphthoyloxy)-4-oxo-β-ionone **17**

Into a suitable reaction vessel under nitrogen are loaded 4.0 g of 3-hydroxy-4-oxo-β-ionone prepared in example 8 (18 mmol theoretical) dissolved in 14 mL of toluene, 2.4 mL of triethylamine (17.2 mmol) and 0.05 g of 4-dimethylaminopyridine; 2.34 mL of 1-naphthoyl chloride (20.3 mmol) dissolved in 5 mL of methylene chloride is added dropwise at 20-25° over 30' and the mixture stirred at 20-25°C for 3-4 hours. Upon completion of the reaction (as judged by HPLC), 10 mL of water are added and the mixture heated at 40°C for 30'. The p-chlorobenzoic anhydride by-product is eliminated by filtration while hot. The organic phase

is separated and washed with 15 mL of 5% acetic acid and subsequently with 15 mL of 5% sodium bicarbonate. The organic phase is concentrated to residue under vacuum and the resulting oil purified by silica gel column chromatography (eluent heptane/t-butyl methyl ether 6:4), to give 1.5 g of 3-(1-naphthoyloxy)-4-oxo-β-ionone (25% with respect to 4-oxo-β-ionone) as a yellow solid with purity of 90% (as judged by GC) and m.p. = 92°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.23 (s, 3H, CH_3 (1_a) ring) ; 1.46 (s, 3H, CH_3 (1_b) ring) ; 1.89 (d, 1.2 Hz, 3H, CH_3(5)ring); 2.22-2.34 (m, 2H, CH_2 (2) ring) ; 2.36 (s, 3H, CH_3 chain); 5.93 (dd, 1H, 6.9 Hz, 12.9 Hz, CH(3)ring); 6.25 (d, 1H, 15.2 Hz, CH_{vin} C=O) ; 7.24 (dd, 1H, 1.1 Hz, 15.2 Hz, CH_{vin} chain); 7.48-7.65 (m, 3H, $CH^{5,6,7}$ naph. ring) ; 7.90-7.87 (m, 1H, CH^3 naph. ring) ; 8.04-8.02 (m, 1H, CH^4 naph. ring) ; 8.28-8.26 (dd, 1H, 1.2 Hz, 7.2 Hz, CH^8 naph. ring) ; 8.95-8.92 (m, 1H, CH^2 naph. ring)

^{13}C-NMR (75 MHz, $CDCl_3$) : δ (ppm) = 13.7; 25.9; 28.2; 30.1; 37.0; 42.7; 71.3; 124.5; 125.8; 126.2; 126.8; 127.7; 128.4; 130.3; 130.4; 131.3; 133.5; 133.7; 134.1; 139.3; 157.2; 166.8; 193.7; 197.1

Example 9: 3-(2-bromobenzoyloxy)-4-oxo-β-ionone

Into a suitable reaction vessel under nitrogen are loaded 8.0 g of oil originating from the previous reaction (32 mmol theoretical) dissolved in 40 mL of toluene, 4.5 mL of triethylamine (32 mmol) and 0.05 g of 4-dimethylaminopyridine; 3.6 mL of 2-bromobenzoyl chloride (27.5 mmol) dissolved in 5 mL of toluene is added dropwise at 20-25° over 30' and the mixture stirred at 20-25°C for 3-4 hours. Upon completion of the reaction (as judged by HPLC), 10 mL of water are added and the mixture heated at 40°C for 30'. The p-chlorobenzoic anhydride by-product is eliminated by filtration while hot. The organic phase is separated and washed with 15 mL of 5% acetic acid and subsequently with 15 mL of 5% sodium bicarbonate. The organic phase is concentrated to residue under vacuum and the resulting oil purified by silica gel column chromatography (eluent heptane/t-butyl methyl ether 6:4), to give 3.8 g of 3-(2-bromobenzoyloxy)-4-oxo-β-ionone (30% with respect to 4-oxo-β-ionone) as a yellow oil with purity of 96% (as judged by GC).

Example 10: [5-(4-hydroxy-2,6,6-trimethyl-3-oxo-1-cyclohexen-1-yl)-3-methyl-2,4-pentadienyl]triphenylphosphonium bromide "C_{15}-Wittig salt" 2

Into a suitable reaction vessel, under nitrogen, is loaded 35 mL of 5% ethinylmagnesium chloride (17.5 mmol) in toluene and THF (Chemetall), the mixture is cooled to -10°C and a solution containing 5.0 g of 3-(4-chlorobenzyloxy)-4-oxo-β-ionone (13.8 mmol) in toluene and THF is added dropwise. The mixture is stirred until the reaction is completed and then quenched with 40 mL of 10% acetic acid. The mixture is stirred, and then the phases allowed to separate, then the organic phase is washed with 25 mL of 5% $NaHCO_3$. The mixture is then evaporated to residue and then taken up with 50 mL of methanol. The solution is loaded into a boiler along with 8.64 mL of a 0.75% w/v solution of dimethylethanolamine in hexane, 8.5 mL of a solution of 0.0125% 1,2-bis-(hydroxyethylthio)-ethanol in ether and 150 mg of Lindlar's catalyst. The mixture is hydrogenated at 1 bar at RT. The catalyst is removed by filtration, the solution is cooled in an ice bath and 0.55 g of sodium hydroxide added. The mixture is left to react until the complete disappearance of the reagent and the reaction neutralised with 0.9 mL of acetic acid. The mixture is concentrated to residue and the oil is taken up with 25 mL of toluene. The solution is cooled in an ice bath, and 1.1 mL of 62% HBr (14.3 mmol) in water added

dropwise, and the mixture left stirring until completion of the reaction. 2.5 mL of 12% sodium carbonate is added and the mixture stirred at RT, the phases are separated and the aqueous phase extracted with 5 mL of toluene. The organic solution is made to react with a mixture containing 3.0 g of triphenylphosphine (11 mmol) in 6.0 mL of methylene chloride. The mixture is stirred at RT for 18 hours. The mixture is then cooled to 0°C, filtered, and the solid washed with 5.0 mL of toluene. 5.0 g (65%) of C_{15}-Wittig salt with a purity of 94% (HPLC A%) are obtained.

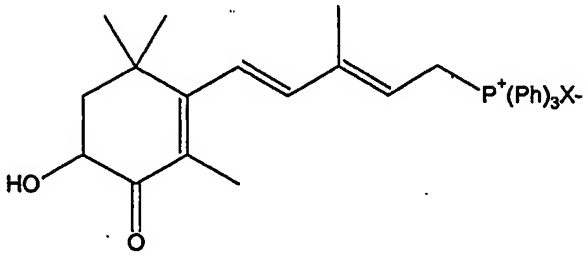
Example 11: Astaxanthin 1

Into a suitably inertised reaction vessel are loaded 5.0 g of C_{15}-Wittig salt (2) (8.4 mmol), 2,7-dimethylocta-2,4,6-trien-1,8-dialdehyde (3) (3.6 mmol) and 3.2 mL of butylene oxide in 25 mL of isopropanol. The reaction is kept refluxing for 18 hours, and subsequently the solid is filtered out. The crude product is isomerised by three successive rounds of re-crystallisation: the dark solid is dissolved in 25 mL of methylene chloride, then the solution is refluxed and the solvent exchanged by distillation at atmospheric pressure with 36 mL of methanol. This procedure is repeated, and the third re-

crystallisation is performed using heptane in place of the methanol. 1.8 g (80%) of Astaxanthin are obtained with a purity of 96% (HPLC A%).

CLAIMS

1. A process for the preparation of astaxanthin by means of the preparation of the intermediate of formula:



where X is selected from Cl, Br or I;

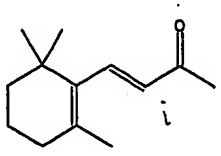
comprising the steps of:

a) oxidising the β-ionone to give the corresponding 4-oxo-β-ionone;

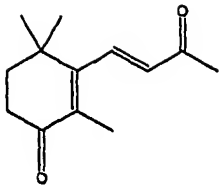
b) transforming the 4-oxo-β-ionone obtained in part a) into 3-hydroxy-4-oxo-β-ionone and/or an ester thereof;

c) transforming the 3-hydroxy-4-oxo-β-ionone and/or the ester thereof into a C_{15}-Wittig salt, and then into astaxanthin;

wherein in step a) the oxidation of the β-ionone



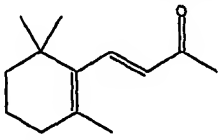
to give the 4-oxo-β-ionone:



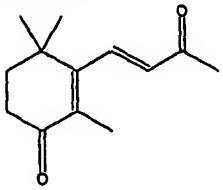
the oxidant used is an alkaline metal or alkaline earth metal bromate in the presence of iodine or an alkaline metal or alkaline earth metal iodide.

2. The process according to claim 1 wherein X is bromine.

3. The process according to claims 1 or 2 wherein in step a) the oxidation of a β-ionone



to give the 4-oxo-β-ionone:



the alkaline metal or alkaline earth metal bromide in the presence of iodine or an alkaline metal or alkaline earth metal iodide are used in an acidic aqueous medium and an organic solvent.

4. The process according to any of the claims 1 to 3 wherein in step a) the bromate is selected from potassium bromate, calcium bromate and sodium bromate, preferably sodium bromate.

5. The process according to any of the claims 1 to 4 wherein in step a) the quantity of bromate is between 0.5 and 1.5 equivalents, preferably between 0.9 and 1.1 equivalents.

6. The process according to any of the claims 1 to 5 wherein in step a) the iodide is selected from sodium iodide and potassium iodide.

7. The process according to any of the claims 1 to 6 wherein in step a) the quantity of iodide is between 0.05 and 1.0 equivalents, more preferably between 0.05 and 0.2 equivalents.

8. The process according to any of the claims 1 to 7 wherein in step a) the organic solvent is selected from aliphatic and aromatic hydrocarbons, ethers and esters, chlorinated hydrocarbons, alcohols and polar aprotic solvents, preferably from hexane, cyclohexane, toluene, t-butyl methyl ether, THF, ethyl acetate, isopropyl acetate, methylene chloride, chloroform, chlorobenzene, dimethyl sulphoxide and methanol, more preferably methylene chloride.

9. The process according to any of the claims 1 to 8 wherein in step a) depending on the organic solvent used, the reaction is carried out at a temperature between 0 and 100°C, preferably between 20 and 70°C, more preferably between 30 and 40°C.

10. The process according to any of the claims 1 to 9 wherein in step a) the aqueous acidic medium is constituted by dilute aqueous solutions of mineral or organic acids, acid salts or a mixture of an acid and its corresponding salt so as to form a buffer solution.

11. The process according to claim 10 wherein the acid is an inorganic acid, preferably selected from sulphuric acid, hydrochloric acid, phosphoric acid, sodium bisulphate, more preferably sodium bisulphate, or an organic acid, preferably selected from acetic acid, formic acid and citric acid.

12. The process according to claims 10 or 11 wherein the acid is used in quantities between 0.1 and 1.0 equivalents, preferably between 0.1 and 0.4 equivalents.

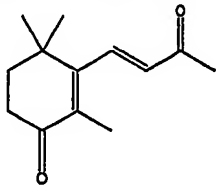
13. The process according to any of the claims 1 to 12, wherein in step a) the reaction is carried out by adding the bromate solution onto the mixture constituted by a β-ionone dissolved in the organic solvent and an aqueous solution of iodide and acid.

14. The process according to any of the claims 1 to 13, wherein in step a) the 4-oxo-β-ionone is purified by crystallisation from an apolar organic solvent, preferably selected from pentane, hexane, heptane, or

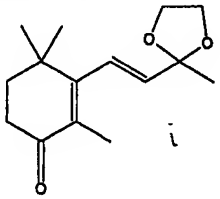
a mixture of the isomers thereof, more preferably a heptane isomer mixture.

15. The process according to any of the claims 1 to 14 wherein step b) consists of the step of:

b1) reacting the 4-oxo-β-ionone:



with ethylene glycol in the presence of an acid catalyst and a dehydrating agent in order to obtain the 4-oxo-β-ionone monoketal of formula:



16. The process according to claim 15 wherein step b) further comprises the step of:

b2) oxidising the monoketal obtained from step b1) with lead tetra-acetate to give the 3-acetoxy-4-oxo-β-ionone monoketal;

b3) de-protecting the 3-acetoxy-4-oxo-β-ionone monoketal by treating the reaction mixture with an aqueous acid to give the 3-acetoxy-4-oxo-β-ionone.

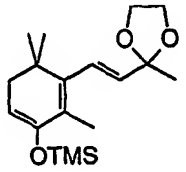
17. The process according to claims 15 or 16, wherein in step b1) the acid catalyst is an inorganic or organic acid, preferably selected from sulphuric,

hydrochloric, hydrobromic, methanesulphonic and p-toluenesulphonic acid, more preferably p-toluenesulphonic acid.

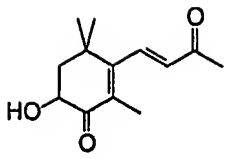
18. The process according to any of the claims 15 to 17, wherein in step b1) the dehydrating agent is an orthoformate or an orthoacetate, more preferably trimethyl orthoformate.

19. The process according to claim 15 wherein step b) further comprises the step of:

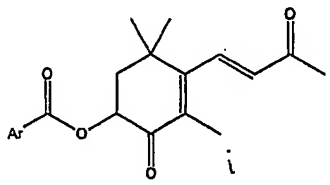
b2) reacting the 4-oxo-β-ionone 9-ethylene ketal, obtained from step b), with a silanising agent and an organic or organometallic base in order to obtain the 4-trimethylsilyloxy-β-ionone 9-ethylene ketal of formula



b3) reacting the 4-trimethylsilyloxy-β-ionone 9-ethylene ketal with a peracid, a peroxide or a hydroperoxide and subsequently treat the reaction mixture with an aqueous acid in order to obtain the 3-hydroxy-4-oxo-β-ionone of formula:



b4) reacting the 3-hydroxy-4-oxo-β-ionone with a compound of formula ArCOX, in cui Ar is an optionally substituted aryl or heteroaryl group, and X is selected from halogen and R_1COO-, wherein R_1 is an optionally substituted alkyl or aryl group, identical or otherwise to Ar, to give the corresponding ester:



20. The process according to any of the claims 1 to 19 wherein step c) consists of the steps of:

c1) transforming the ester of 3-hydroxy-4-oxo-b-ionone into the corresponding tertiary alcohol intermediate;

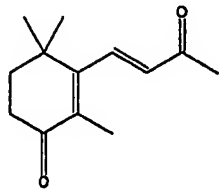
c2) hydrolysing the ester group;

c3) rearranging the tertiary alcohol to the corresponding allyl halide;

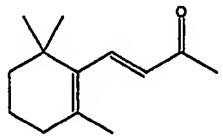
c4) treating the halide obtained from step c3) with triphenylphosphine to give the C_{15}-Wittig salt;

c5) condensing the C_{15}-Wittig salt with C_{10}-dialdehyde to give astaxanthin.

21. The process for the preparation of 4-oxo-β-ionone of formula:

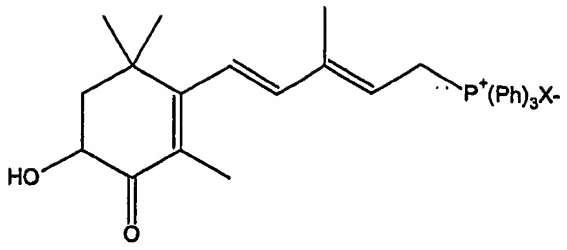


starting from the β-ionone of formula



by oxidation with an alkaline metal or alkaline earth metal bromate in the presence of iodine or an alkaline metal or alkaline earth metal iodide, characterised in that said bromate is used in quantities between 0.5 and 1.5 equivalents.

22. A process for the preparation of astaxanthin by means of the preparation of the intermediate of formula:



where X is selected from Cl, Br or I;

comprising the steps of:

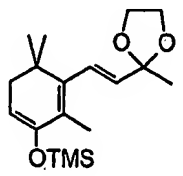
a) oxidising the β-ionone to give the corresponding 4-oxo-β-ionone;

b) transforming the 4-oxo-β-ionone obtained in part a) into an ester of 3-hydroxy-4-oxo-β-ionone;

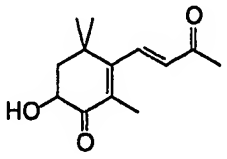
c) transforming the ester of 3-hydroxy-4-oxo-β-ionone into the C_{15}-Wittig salt and then into astaxanthin;

wherein step b) consists of, among others, the following steps:

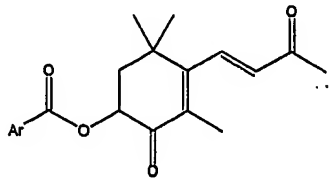
b2) reacting the 4-oxo-β-ionone 9-ethylene ketal with a silanising agent and an organic or organometallic base in order to obtain the 4-trimethylsilyloxy-β-ionone 9-ethylene ketal of formula



b3) reacting the 4-trimethylsilyloxy-β-ionone 9-ethylene ketal with a peracid, a peroxide or a hydroperoxide and subsequently treat the reaction mixture with an aqueous acid in order to obtain the 3-hydroxy-4-oxo-β-ionone of formula:

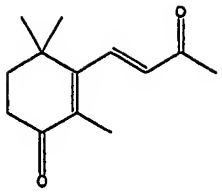


b4) reacting the 3-hydroxy-4-oxo-β-ionone with a compound of formula ArCOX, in cui Ar is an optionally substituted aryl or heteroaryl group, and X is selected from halogen and R_1COO-, wherein R_1 is an optionally substituted alkyl or aryl group, identical or otherwise to Ar, to give the corresponding ester:

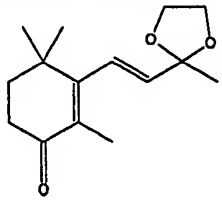


23. The process according to claim 22 wherein step b) comprises the step of:

b1) reacting the 4-oxo-β-ionone:



with ethylene glycol in the presence of an acid catalyst and a dehydrating agent in order to give the 4-oxo-β-ionone 9-ethylene ketal of formula:



24. The process according to claims 22 or 23, wherein in step b2) the silanising agent is selected from chlorotrimethylsilane, bromotrimethylsilane, iodotrimethylsilane and hexamethyldisilazane, preferably chlorotrimethylsilane.

25. The process according to any of the claims 22 to 24, wherein in step b2) the organic or organometallic base is selected from triethylamine, diisopropylethylamine, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, preferably lithium diisopropylamide, also prepared *in situ* by reacting diisopropylamine and n-butyl lithium.

26. The process according to any of the claims 22 to 25, wherein in step b3) the peracid is selected from

peracetic acid, m-chloroperbenzoic acid, potassium monoperoxyphthalate, preferably peracetic acid.

27. The process according to any of the claims 22 to 26, wherein step b3) is carried out in an organic solvent immiscible with water, preferably selected from aliphatic and aromatic hydrocarbons and chlorinated hydrocarbons.

28. The process according to claim 27, wherein the organic solvent is selected from toluene, xylene, methylene chloride, chloroform, more preferably toluene.

29. The process according to any of the claims 22 to 28, wherein in step b4) X is halogen.

30. The process according to any of the claims 22 to 29 for the preparation of 3-(4-chlorobenzyloxy)-4-oxo-β-ionone, wherein in step b4) the compound of formula ArCOX is 4-chlorobenzoyl chloride.

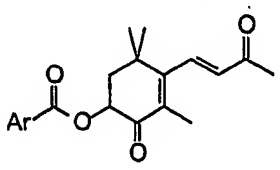
31. The process according to any of the claims 22 to 30 for the preparation of 3-(1-naphthoyloxy)-4-oxo-β-ionone, wherein in step b4) the compound of formula ArCOX is 1-naphthoyl chloride.

32. The process according to any of the claims 22 to 31, wherein the product obtained from step b4) is purified by crystallisation from alcoholic solvents,

preferably selected from methanol, ethanol and isopropanol.

33. The process according to any of the claims 22 to 32 wherein in step a) the β-ionone is oxidised to 4-oxo-β-ionone by means of pyridinium chlorochromate, or ceric ammonium nitrate and iodine, or chromium(VI) derivatives.

34. Compounds of general formula



wherein Ar is an optionally substituted aryl or heteroaryl group.

35. The compounds according to claim 34 wherein Ar is a phenyl group, optionally mono- or polysubstituted with groups preferably selected from alkoxyl, halogen, nitro, cyano and methyl, or a polyaryl group, preferably naphthyl.

36. The compounds according to claims 34 or 35 wherein Ar is a phenyl group mono-substituted with halogen or nitro, preferably with a chlorine atom.

37. 3-(4-chlorobenzoyloxy)-4-oxo-β-ionone

38. 3-(1-naphthoyloxy)-4-oxo-β-ionone

39. Use of the compounds claimed in claims 34 to 38 for the preparation of Astaxanthin.